UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,733		CHARLES ZUKER	02307E-085110US	6739

7590 11/10/2004

ANNETTE S PARENT
TOWNSEND AND TOWSEND AND CREW
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,733	ZUKER, CHARLES	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-17,19,20 and 22-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-17, 19, 20, 22-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed August 17, 2004. Claims 1, 3-17, 19, 20, and 22-36 are pending. Claims 2, 18, 21, 37 and 38 have been cancelled. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-17, 19, 20, and 22-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Byk in view of Zuker (reference "AG") and Zuker (GenBank Accession No. M17718; reference "AE").

Byk teaches a method of screening *in vitro* for compounds which modulate RDGC activity. Specifically, Byk teaches a method comprising providing a first sample of eye membranes containing wild-type RDGC and a second sample of eye membranes containing mutant RDGC; contacting the sample with a compound (such as calcium or arrestin) which is suspected of having the ability to modulate RDGC GPCR phosphatase activity, and detecting RDGC GPCR phosphatase activity by means of a phosphorylation assay that is conducted by measuring mobility on an electrophoretic gel (see figures 2 and 5, and page 1909). Byk teaches that the GPCR rhodopsin is a major substrate for RDGC phosphatase (page 1908) and specifically exemplifies methods

which monitor calcium and arrestin for their ability to modulate dephosphorylation of rhodopsin by RDGC. Byk does not teach performing a signal transduction assay to detect phosphatase activity, does not teach applying the screening method to one performed *in vivo*, and does not teach the use of recombinant RDGC or recombinant GPCR.

Zuker teaches a method of measuring membrane potential changes in intact *Drosophila* photoreceptor cells and calcium changes in *Drosophila* transgenic for a particular rhodopsin (Figure 4). At page 575, Zuker states that "the genetic dissection of this [phototransduction] pathway in humans and flies has provided fundamental insight into the molecular and cellular basis of inherited retinal disorders". Zuker (page 575) further states that "It is here where the study of phototransduction in *Drosophila* offers unprecedented versatility. The study of this signal cascade in the fruit fly *Drosophila melanogaster* makes it possible to use powerful molecular genetic techniques to identify novel transduction molecules and then to examine the function of these molecules *in vivo*, in their normal cellular and organismal environment". Furthermore, Zuker (GenBank Accession No. M17718) teaches the isolated nucleic acid sequence of *Drosophila* RDGC, which can be used for synthesizing recombinant RDGC and for generating transgenics expressing RDGC.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Byk so as to have used recombinant RDGC and rhodopsin in place of native RDGC and rhodopsin since nucleic acids encoding these proteins were well known in the art at the time the invention was

made and the use of nucleic acids to synthesize recombinant proteins was conventional in the art. Accordingly, modification of the method of Byk so as to have used recombinant RDGC and rhodopsin would have provided a convenient means for obtaining sufficient quantities of protein to use for in vitro assays. However, it is also noted that the recitation in the claims of "recombinant" does not further distinguish the claimed RDGC phosphatase over the naturally occurring phosphatase. The claims and specification do not recite any identifying characteristics which would distinguish recombinant RDGC phosphatase from naturally occurring RDGC phosphatase. In addition, with respect to claims 9-13, 15-17, 19, 20, and 22-38, Zuker exemplifies transgenic Drosophila which express recombinant rhodopsin and teaches the benefits of using transgenic Drosophila to analyze in vivo activities. It would have been obvious to one of ordinary skill in the art to have transformed isolated cells, particularly insect cells, with expression vectors comprising rhodopsin and RDGC nucleic acids since Byk teaches that rhodopsin and RDGC proteins are involved in the phototransduction signal cascade and because this would have achieved the advantage of using an isolated system in which the presence of a particular pathway component could be controlled and the expressed proteins would be in an environment similar to the normal cellular environment (i.e., in an insect cell). It is noted that Zuker teaches the advantages of the ability to dissect pathways molecularly. To most closely mimic a natural environment, it would have been desirable and obvious to one of ordinary skill in the art at the time the invention was made to have used whole cells and transgenic organisms in the method of Byk instead of membrane preparations because Zuker teaches that light and calcium

applied to whole cells can be used as methods of screening for compounds which influence the phototransduction pathway (see, for example, Figure 3) and Zuker teaches the importance of assaying molecular mechanisms *in vivo* in their normal cellular and organismal environment.

Response to arguments:

In the response filed August 17, 2004, Applicants traversed this rejection by stating that the Byk reference does not teach that rdgC is required for efficient dephosphorylation in vivo. It is stated that Zuker teaches only that rdgc "presumably dephosphorylates rhodopsin." Thereby, Applicants conclude that the prior art does not elucidate the in vivo biological role of RDGC phosphatase and thereby one would not have been motivated to have used RDGC phosphatases as a component of a screening system to identify modulators of GPCR-mediated signal transduction. It is argued that without an in vivo context, the skilled artisan would not arrive at the screening methods of the claimed invention. It is also asserted that because a paper was published in Science after the priority date of the present application, that this serves as evidence "that those of skill in the art at the time the invention did not consider the in vitro studies and presumptive role of rdgC phosphatase to lead to Applicants' invention."

Applicant's arguments have been fully considered but are not persuasive. Byk teaches that "phosphorylated rhodopsin is a major substrate for the rdgC phosphatase" (see abstract). Byk (page 1910) also teaches that following phosphorylation of rhodopsin and release of arrestin, "p-R then becomes an efficient substrate for rhodopsin phosphatase, which safely reintroduces it to the rhodopsin pool, ready for the

next round of photoexcitation." The reference further states (page 1910) that "(g)enetic analysis of the *Drosophila* mutant rdgC revealed that retinal degeneration is dependent on high levels of activated rhodopsin and placed the site of action of the *rdgC* gene product before phospholipase C." Thereby, Byk clearly teaches that RDGC dephosphorylates rhodopsin. There is absolutely nothing in Byk which would suggest to the ordinary artisan that RDGC will not act to dephophosphorylate rhodopsin in vivo.

Additionally, Zuker (Figure 1) illustrates the phototransduction pathway in *Drosophila* photoreceptors, including the step in which rhodopsin is dephosphorylated by RDGC phosphatase and the role of this step in the GPCR-mediated signal transduction pathway. While Applicants point out that Zuker states that rhodopsin is "presumably dephosphorylated by the rdgC-encoded phosphatase," the illustration set forth in Figure 1 of Zuker shows that rhodopsin is dephosphorylated by RDGC phosphatase. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). Based on the teachings of Zuker, the ordinary artisan would have had more than a reasonable expectation that rhodopsin is dephosphorylated by RDGC in vivo. The term "presumptive" is defined by Webster's dictionary as meaning "Providing a reasonable basis for acceptance or belief." Accordingly, the ordinary artisan reading the teachings of Zuker would conclude that this reference did in fact teach that rhodopsin is dephosphorylated by RDGC in vivo. Thereby, the combined teachings of Byk and Zuker do teach that RDGC dephosphorylates rhodopsin and that this is an essential

step in the GPCR-mediated signal transduction pathway. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated a method for identifying additional compounds which modulate RDGC phosphatase activity as a means for identifying compounds which potentially effect GPCR-mediated signal transduction and thereby compounds which effect phototransduction.

Further, the fact that the Vinos reference was published after the filing date of the present application does not indicate that the ordinary artisan would not have arrived at the present invention based upon the teachings of Byk and Zuker. This is equivalent to arguing that publication of a reference indicates that the teachings of the reference are unobvious over the prior art. Clearly this is not the standard for determining patentability and not the standard for determining whether a paper is accepted by a journal and published. There is no case law which would support a conclusion that patentability should be evaluated based on whether a reference is published following the filing date of an application. Moreover, Vinos confirms the findings of Byk and Zuker by showing that RDGC does dephosphorylate rhodopsin in vivo. Vinos states "**As expected**, in white-eyed control flies, Rh1 was phosphorylated in a blue light-dependent manner, whereas subsequent exposure to orange light promoted its dephosphorylation" (emphasis added). Thereby, the Vinos reference serves as evidence that the teachings of Byk and Zuker were in fact correct and that the ordinary artisan would have had more than a reasonable expectation of success at generating an in vivo method for screening for modulators of RDGC GPCR phosphatase activity. Additionally, the teachings of

Vinos are not limited to a showing that RDGC dephosphorylates rhodopsin in vivo. Rather, the reference also addresses RDGC mutants and the phenotypes of these mutants. Thereby, acceptance and publication of this reference does not allow one to drawn any negative conclusions regarding the teachings of Byk and Zuker. Applicants reliance on the Vinos paper as evidence of the nonobviousness of the present invention is based only on opinion and is not substantiated by any pertinent evidence.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Carla Myers
November 9, 2004

CARLA J. MYERS
PRIMARY EXAMINER